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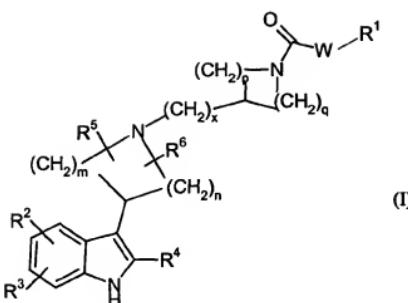
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*[Continued on next page]***(54) Title:** 3-SUBSTITUTED INDOLES AS CHEMOKINE ANTAGONISTS

(57) Abstract: A compound of the formula (I): in which: R¹ is (C₁₋₆)alkyl, optionally substituted aryl or optionally substituted heteroaryl; R² and R³ which may be the same or different are selected from the group consisting of hydrogen, halogen, cyano(C₁₋₆)alkyl, (C₃₋₇)cycloalkyl, (C₁₋₆)alkoxy, halo(C₁₋₆)alkyl, hydroxy, amino, mono- or di-(C₁₋₆)alkylamino, acylamino, nitro, carboxy, (C₁₋₆)alkoxycarbonyl, (C₁₋₆)alkenylloxycarbonyl, (C₁₋₆)alkoxycarbonyl(C₁₋₆)alkyl, carboxyl(C₁₋₆)alkyl, (C₁₋₆)alkylcarbonyloxy, carboxy(C₁₋₆)alkyloxy, (C₁₋₆)alkyloxycarbonyl(C₁₋₆)alkoxy, (C₁₋₆)alkylthio, (C₁₋₆)alkylsulphonyl, (C₁₋₆)alkylsulphonyl, sulphamoyl, mono- and di-(C₁₋₆)alkylsulphonyl, carbamoyl, mono- and di-(C₁₋₆)alkylcarbamoyl, ureido, (C₁₋₆)alkylsulphonamido, aroylsulphonamido, aryl, aryl(C₁₋₆)alkyl, aryl(C₂₋₆)alkoxy, aroyloxy and heterocycl; R⁴ is hydrogen or C₁₋₆alkyl; R⁵ and R⁶ which may be the same or different are hydrogen

or C₁₋₆alkyl, or together with the carbon atoms of the ring to which they are attached from the bridging 5- to 7 membered ring; W is a bond, C₁₋₆alkylene optionally substituted by C₀₋₆alkyl, CH₂O, CH₂S OR trans-(E)-CR=Y- in which R² is hydrogen or (C₁₋₆)alkyl and Y is a bond, trans-(E)-CH=CH-, or CO; m and n are each integers from 1 to 3; p and q are each independently 1 or 2; and x is an integer from 1 to 4; or a pharmaceutically acceptable salt thereof. For use in the manufacture of a medicament for use in the treatment of inflammatory conditions with monocyte and/or lymphocyte involvement.

WO 02/079190 A1



For two-letter codes and other abbreviations, refer to the "Guidance Notes on Codes and Abbreviations" appearing at the beginning of each regular issue of the PCT Gazette.

3-SUBSTITUTED INDOLES AS CHEMOKINE ANTAGONISTS

The present invention relates to a novel class of 3-substituted indoles which are antagonists of the chemokine MCP-1 (CCR2B) receptor, processes for their preparation
5 and their use in therapy.

Chemokines are structurally and functionally related 8 to 10 kD polypeptides, involved in the recruitment of white blood cells into areas of inflammation and their subsequent activation (Miller, M.D. and Krangel, M.S. (1992) *Crit. Rev. Immunol.* **12**, 17-46; 10 Baggolini, M., Dewald, B. and Moser, B. (1994) *Adv. Immunol.* **55**, 97-179). In addition, some chemokines are able to regulate the proliferative potential of hematopoietic progenitor cells, endothelial cells and certain types of transformed cells (Oppenheimer, J.J., Zachariae, C.O.C., Mukaida, N., and Matsushima, K. (1991) *Ann. Rev. Immunol.* **9**, 617-648; Schall, T.J. (1991) *Cytokine* **3**, 165-183). Based on whether 15 the first two cysteine moieties are separated by one amino acid residue or are adjacent, chemokines belong to the α - or CXC chemokine family (e.g. interleukin IL-8 or the β - or CC chemokine family (e.g. RANTES and MCP-1).

More recently, two further classes of chemokines have been discovered: the C chemokine 20 family exemplified by lymphotactin (Science, 1994, 266, 1395-1399) and the CX3C chemokine family exemplified by fractalkine/neurotactin (Nature, 1997, 385, 640-44 and Nature, 1997, 387, 611-17)

Chemokines play a key role in the accumulation of various cell types, including 25 neutrophils, monocytes, T-lymphocytes, basophils and fibroblasts at sites of inflammation. These chemokines are implicated in both acute and chronic inflammatory disease states, including rheumatoid arthritis, inflammatory bowel disease, atherosclerosis, asthma, restenosis, psoriasis, various respiratory syndromes, for instance asthma and idiopathic pulmonary fibrosis, and also contribute towards modulation of 30 angiogenesis and fibroplasia. Chemokines are also implicated in various infectious diseases including viral, bacterial and parasitai infections, stroke, sarcoidosis, chronic contact dermatitis, as well as organ transplant rejection.

Chemokines express their biological responses through interaction with chemokine 35 receptors (Horuk, R. and Peiper, S.C. (1995) *Exp. Opin. Ther. Patents* **5**, 1185-1200). Several chemokine receptors have already been cloned, for instance, the following human CXC chemokine receptors:

- (a) the receptors for IL8 (CXCR1) and IL8/ELR chemokines, (CXCR2, Holmes, W.E., Lee, J., Kuang, W.J., Rice, G.C. and Wood, W.I. (1991) *Science* **253**, 1278-1280; Murphy, P.M. and Tiffany, H.L. (1991) *Science* **253**, 1280-1283);
- 5 (b) a receptor for IP10/Mig (CXCR3, Loetscher, M., Gerber, B., Loetscher, P., Jones, S.A., Piali, L., Clark-Lewis, I., Baggolini, M., and Moser, B. (1996) *J. Exp. Med.* **184**, 963-969.); and
- (c) a receptor for SDF-1 (CXCR4 or LESTR, Bleul, C.C., Farzan, M., Choe, H., Parolin, C., Clark-Lewis, I., Sodroski, J., Springer, T.A. (1996) *Nature*, **382**, 829-836.)
- 10 In addition, the following human CC chemokine receptors have also been cloned:
- (a) MIP-1 α /RANTES receptor (CCR-1, Neote, K., Digregorio, D., Mak, J.K., Horuk, R. and Schall, T.J. (1993) *Cell* **72**, 415-425; Gao, B. J-L., Kuhns, D.B., Tiffany, H.L., McDermott, D., Li, X., Francke, U. and Murphy, P.M. (1993) *J. Exp. Med.* **177**, 1421-1427);
- 15 (b) MCP-1A and B receptors (CCR-2A and B, Charo, I.F., Myers, S.J., Herman, A., Franci, C., Connolly, A.J. and Coughlin, S.R. (1994) *Proc. Natl. Acad. Sci. USA* **91**, 2752-2756; Yamagami, S., Tokuda, Y., Ishii, K., Tanaka, T. and Endo, N. (1994) *Biochem. Biophys. Res. Commun.* **202**, 1156-1162);
- (c) the eotaxin/RANTES receptor (CCR-3, Combadiere, C., Ahuja, S.K. and Murphy, P.M. (1995) *J. Biol. Chem.* **270**, 16491-16494; Daugherry, D.L., Siciliano, S.J., DeMartino, J.A., Malkowitz, L., Sirotina, A. and Springer, M.S. (1996) *J. Exp. Med.* **183**, 2349-2354; Kitaura, M., Nakajima, T., Imai, T., Harada, S., Combadiere, C., Tiffany, H.L., Murphy, P.M. and Yoshie, O. (1996) *J. Biol. Chem.* **271**, 7725-7730);
- 20 (d) the promiscuous receptor on basophils (CCR-4, Power, C.A., Meyer, A., Nemeth, K., Bacon, K.B., Hoogewerf, A.J., Proudfoot, A.E.I. and Wells, T.N.C. (1995) *J. Biol. Chem.* **270**, 19495-19500);
- (e) a new MIP-1 α /MIP-1 β /RANTES receptor (CCR-5, Samson, M., Labbe, O., Mollereau, C., Vassart, G. and Parmentier, M. (1996) *Biochemistry* **35**, 3362-3367.);
- (f) a new receptor for LARC (CCR6, Baba, M., Imai, T., Nishimura, M., Kakizaki, M., Takagi, S., Hieshima, Nomiyuki, H., and Yoshie, O. (1997) *J. Biol. Chem.* **272**, 14893-14898.);
- (g) a new receptor for ELC/exodus3 (CCR7, Yoshida, R., Imai, T., Hieshima, K., Kusuda, J., Baba, M., Kitaura, M., Nishimura, M., Kakizaki, M., Nomiyama, H., and Yoshie, O. (1997) *J. Biol. Chem.* **272**, 13803-13809.); and
- 30 (h) a new receptor for I-309 (CCR8, Samson, M., Stordeur, P., Labbe, O., Soularue, P., Vassart, G., and Parmentier, M. (1997) *Eur. J. Immunol.* **26**, 3021-3028; Tiffany, H.L., Lautens, LL, Gao,J-L, Pease, J., Locati, M., Combadiere, C., Modi, W., Bonner, T.I. and

Murphy, P.M. (1997) *J Exp. Med.* 186, 165-170; Stuber-Roos, R., Loetscher, M., Legner, D.F., Clark-Lewis, I., Baggolini, M. and Moser, B. (1997) *J. Biol. Che.* 272, 17251-17254).

- 5 Recently the receptor for the newly described CX3C chemokine, fractalkine/neurotactin, has also been identified (Imai, T., Hieshima, K., Haskell, C., Baba, M., Nagira, M., Nishimura, M., Kakizaki, M., Takagi, S., Nomiyama, H., Schall, T.J., Yoshie, O. (1997) *Cell* 91, 521-530).
- 10 Chemokine receptors belong to the group of 7 transmembrane (7TM) spanning receptors and their signal transduction pathway involves pertussus toxin-sensitive G-protein and a rise in $[Ca^{2+}]_i$. Although details about the molecular events are still incomplete, a complex array of intracellular signals ultimately lead to leukocyte activation and chemotaxis (Premack, B.A. and Schall, T.J. (1996) *Nature Medicine* 2, 1174-1178).
- 15

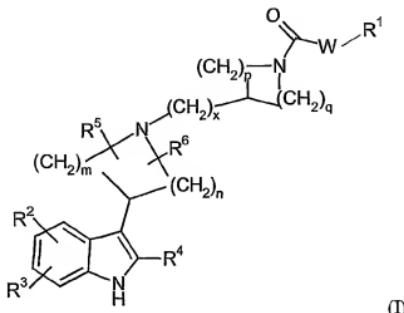
Chemokine receptors are divided into at least three sub-families, the CXC chemokine receptors (CXCR), the CC chemokine receptors (CCR) and the CX3CR, based on their selectivity for either CXC, CC, CX3C chemokines. Ligand cross-selectivity that is CXCRs that bind CC chemokines or *vice versa*, is not observed. 20 Chemokine receptors consist of 350-368 amino acids and the sequence identity amongst members of the receptor sub-families varies widely, from about 36-77%. Most chemokine receptors recognise more than one chemokine and many chemokines, including IL-8, RANTES, MIP-1 α and the MCPs, bind to more than 25 one receptor (Roos *et al*, *J Biol Chem*, 1997, 272 (28), 17521).

EP-A-0 324 431 (Fujisawa Pharm KK) describes a group of N-substituted indolyl-piperidine derivatives having anti-allergic activity. The N substituent is A-NH-CO-B-R₁ in which R₁ is aryl substituted by optionally protected hydroxy, halo and /or lower 30 alkoxy, A is lower alkylene and B is lower alkylene. In exemplified compounds, A is CH₂CH₂ whilst B is generally butadienyl.

A class of MCP-1 receptor antagonists has recently been disclosed (WO 98/06703, Warner Lambert).

35 We have now found a new class of indole compounds that are MCP-1 (CC2RB) receptor antagonists.

Accordingly, the present invention provides a compound of the formula (I):



5 in which:

R¹ is (C₁₋₆)alkyl, optionally substituted aryl or optionally substituted heteroaryl;

R² and R³ which may be the same or different are selected from the group consisting of hydrogen, halogen, cyano, (C₁₋₆)alkyl, (C₃₋₇)cycloalkyl, (C₁₋₆)alkoxy, halo(C₁₋₆)alkyl, hydroxy, amino, mono- or di-(C₁₋₆)alkylamino, acylamino, nitro,

10 carboxy, (C₁₋₆)alkoxycarbonyl, (C₁₋₆)alkenyloxycarbonyl,

(C₁₋₆)alkoxycarbonyl(C₁₋₆)alkyl, carboxy(C₁₋₆)alkyl, (C₁₋₆)alkylcarbonyloxy,

carboxy(C₁₋₆)alkyloxy, (C₁₋₆)alkoxycarbonyl(C₁₋₆)alkoxy, (C₁₋₆)alkylthio,

(C₁₋₆)alkylsulphinyl, (C₁₋₆)alkylsulphonyl, sulphamoyl, mono- and di-(C₁₋₆)-alkylsulphamoyl, carbamoyl, mono- and di-(C₁₋₆)alkylcarbamoyl, ureido,

15 (C₁₋₆)alkylsulphonamido, arylsulphonamido, aryl, aryl(C₁₋₆)alkyl, aryl(C₁₋₆)alkoxy,

aryloxy and heterocycl;

R⁴ is hydrogen or C₍₁₋₆₎alkyl;

R⁵ and R⁶ which may be the same or different are hydrogen or C₍₁₋₆₎alkyl, or together with the carbon atoms of the ring to which they are attached form a bridging 5-to 7-membered ring;

20 W is a bond, (C₁₋₆)alkylene optionally substituted by (C₁₋₆)alkyl, CH₂O, CH₂S or trans-(E)-CR⁷=CH-Y- in which R⁷ is hydrogen or (C₁₋₆)alkyl and Y is a bond,

trans-(E)-CH=CH-, or CO;

m and n are each integers from 1 to 3;

25 p and q are each independently 1 or 2; and

x is an integer from 1 to 4; or

a pharmaceutically acceptable salt thereof.

Compounds of the formula (I) are antagonists of the MCP-1 (CC2RB) receptor and also inhibit MCP-1 stimulated chemotaxis in monocytes. They are therefore believed to be of use in the treatment of inflammatory diseases with monocyte and/or lymphocyte involvement such as atherosclerosis and arthritis.

5 Representative values of R¹ include pentyl, phenyl, naphthyl, furanyl, pyridyl, thieryl, oxazolyl, chromanyl, indanyl, benzofuranyl, benzothienyl, and indolyl in which the aryl or heteroaryl ring is optionally substituted by 1 or 2 substituents. Preferably R¹ is substituted phenyl.

10 Representative substituents for R¹ include halo, for instance fluoro, chloro or bromo; (C₃-7)cycloalkyl, for instance cyclohexyl; (C₁-6)alkoxy, for instance methoxy; (C₁-6)alkyl, for instance methyl or iso-propyl; halo(C₁-6)alkyl, for instance trifluoromethyl; hydroxy; nitro; acyl amino, for instance acetyl amino; and phenylCO-

15 Representative values of R² include hydrogen, (m)ethyl, methoxy, hydroxy, (m)ethanesulphonamido, amino, methoxycarbonyl, (methyl)aminocarbonyl and ureido. Representative values of R³ include hydrogen or methyl. Preferably, R² is hydrogen or a substituent at the 5-position, for instance 5-OH or 5-NH₂, and R³ is hydrogen.

Preferably, R⁴ is hydrogen or methyl.

20 Preferably, R⁵ and R⁶ is each hydrogen or R⁵ and R⁶ are joined together to form a five membered ring, to give a tropane moiety.

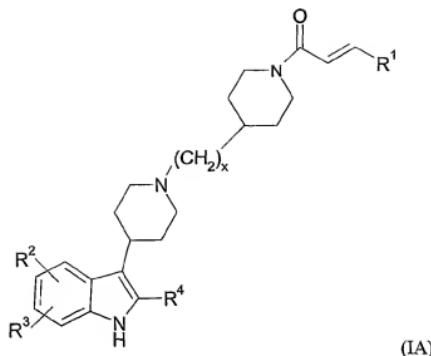
Representative values for n include 1 and 2 and for m include 2. Preferably m and n are each 2, to form a piperidinyl ring.

30 Representative values for p include 1 and 2 and for q include 2. Preferably p and q are each 2, to form a piperidinyl ring with the amide nitrogen.

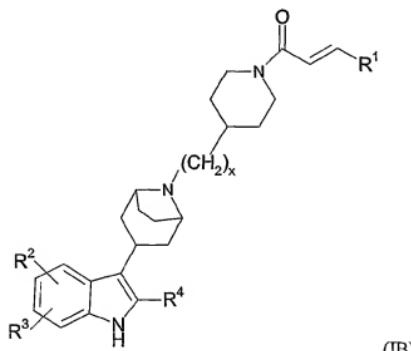
Representative values of x include 1, 2 and 3.

35 Preferably, W is *trans*-(E)-CH=CH-.

Preferred sub-groups of compounds of formula (I) are those of formulae (IA), (IB) :



in which R^2 , R^3 , R^4 , and x are as hereinbefore defined, and R^1 is substituted aryl;



5

in which R^2 , R^3 , R^4 and x are as hereinbefore defined, and R^1 is substituted aryl.

When used herein, the term "alkyl" and similar terms such as "alkoxy" includes all
 10 straight chain and branched isomers. Representative examples thereof include methyl,
 ethyl, *n*-propyl, *iso*-propyl, *n*-butyl, *sec*-butyl, *iso*-butyl, *t*-butyl, *n*-pentyl and *n*-hexyl.

When used herein, the term "aryl" includes, unless otherwise defined, phenyl or naphthyl
 15 optionally substituted with up to five, preferably up to three substituents.

15

Suitable substituents for an aryl group include, for example, and unless otherwise defined, halogen, cyano, (C₁-6)alkyl, (C₃-7)cycloalkyl, (C₁-6)alkoxy, halo(C₁-6)alkyl, hydroxy, amino, mono- or di-(C₁-6)alkylamino, acylamino, nitro, carboxy, (C₁-6)alkoxycarbonyl, (C₁-6)alkenyloxycarbonyl, (C₁-6)alkoxycarbonyl(C₁-6)alkyl,

- 5 carboxy(C₁-6)alkyl, (C₁-6)alkylcarbonyloxy, carboxy(C₁-6)alkyloxy, (C₁-6)alkoxycarbonyl(C₁-6)alkoxy, (C₁-6)alkylthio, (C₁-6)alkylsulphanyl, (C₁-6)alkylsulphonyl, sulphamoyl, mono- and di-(C₁-6)-alkylsulphamoyl, carbamoyl, mono- and di-(C₁-6)alkylcarbamoyl, ureido, (C₁-6)alkylsulphonamido, arylsulphonamido, aryl, aryl(C₁-6)alkyl, aryl(C₁-6)alkoxy and heterocycl.

10

When used herein, the term "heterocycl" or "heterocyclic" includes single or fused aromatic or non-aromatic rings comprising up to four hetero-atoms in the ring selected from oxygen, nitrogen and sulphur and optionally substituted with up to three substituents. Suitably the heterocyclic ring comprises from 4 to 7, preferably 5 to 6, ring atoms. A fused heterocyclic ring system may include carbocyclic rings and need only include one heterocyclic ring.

When used herein, the term "heteroaryl" includes an aromatic heterocyclic ring or ring system, preferably with 5 or 6 ring atoms on each ring.

20

When substituted, a heterocycl group may have up to three substituents. Suitable such substituents include those previously mentioned for an aryl group as well as oxo.

25

When used herein, the terms "halogen" and "halo" include fluorine, chlorine, bromine and iodine and fluoro, chloro, bromo and iodo, respectively.

30

Pharmaceutically acceptable salts include those described by Berge, Bighley, and Monkhouse, *J. Pharm. Sci.*, 1977, 66, 1-19. Such salts may be formed from inorganic and organic acids. Representative examples thereof include maleic, fumaric, benzoic, ascorbic, pamoic, succinic, bismethylenesalicylic, methanesulfonic, ethanesulfonic, acetic, propionic, tartaric, salicylic, citric, gluconic, aspartic, stearic, palmitic, itaconic, glycolic, p-aminobenzoic, glutamic, benzenesulfonic, hydrochloric, hydrobromic, sulfuric, cyclohexylsulfamic, phosphoric and nitric acids.

35

It will be appreciated that certain compounds of the present invention may comprise one or more chiral or stereo centres so that compounds may exist as stereoisomers, including diastereoisomers and enantiomers. The present invention covers all such stereoisomers,

and mixtures thereof, including racemates. In particular, the present invention also covers both Z and E-diastereoisomers arising from the double bond of the cinnamide moiety of compounds of formula (I).

- 5 Since the compounds of the present invention, in particular compounds of formula (I), are intended for use in pharmaceutical compositions, it will be understood that they are each provided in substantially pure form, for example at least 50% pure, more suitably at least 75% pure and preferably at least 95% pure (% are on a wt/wt basis). Impure preparations of the compounds of formula (I) may be used for preparing the more pure forms used in
- 10 10 the pharmaceutical compositions. Although the purity of intermediate compounds of the present invention is less critical, it will be readily understood that the substantially pure form is preferred as for the compounds of formula (I). Preferably, whenever possible, the compounds of the present invention are obtained in crystalline form.
- 15 When some of the compounds of this invention are allowed to crystallise or are recrystallised from organic solvents, solvent of crystallisation may be present in the crystalline product. This invention includes within its scope such solvates. Similarly, some of the compounds of this invention may be crystallised or recrystallised from solvents containing water. In such cases water of hydration may be formed. This
- 20 20 invention includes within its scope stoichiometric hydrates as well as compounds containing variable amounts of water that may be produced by processes such as lyophilisation. In addition, different crystallisation conditions may lead to the formation of different polymorphic forms of crystalline products. This invention includes within its scope all polymorphic forms of the compounds of formula (I).
- 25 Preferred compounds of formula (I) include:
- (E)-3-(3,4-Dichloro-phenyl)-1-{4-[4-(1*H*-indol-3-yl)-piperidin-1-ylethyl]-piperidin-1-yl}-propenone;
- (E)-3-(3,4-Dichloro-phenyl)-1-{4-[4-(1*H*-indol-3-yl)-piperidin-1-ylpropyl]-piperidin-1-yl}-propenone;
- 30 (E)-3-(3,4-Dichloro-phenyl)-1-{4-[4-(1*H*-indol-3-yl)-piperidin-1-ylmethyl]-piperidin-1-yl}-propenone;
- (E)-3-(3,4-Dichloro-phenyl)-1-{4-[4-(1*H*-5-hydroxyindol-3-yl)-piperidin-1-ylethyl]-piperidin-1-yl}-propenone;
- 35 (E)-3-(3,4-Dichloro-phenyl)-1-{4-[4-(1*H*-5-methylindol-3-yl)-piperidin-1-ylethyl]-piperidin-1-yl}-propenone;

- (E)-3-(3,4-Dichloro-phenyl)-1-{4-[4-(1*H*-5-methoxyindol-3-yl)-piperidin-1-ylethyl]-piperidin-1-yl}-propenone;
- (E)-3-(3,4-Dichloro-phenyl)-1-{4-[4-(1*H*-5-methanesulfonamidoindol-3-yl)-piperidin-1-ylethyl]-piperidin-1-yl}-propenone;
- 5 (E)-3-(3,4-Dichloro-phenyl)-1-{4-[4-(1*H*-7-methylindol-3-yl)-piperidin-1-ylethyl]-piperidin-1-yl}-propenone;
- (E)-3-(3,4-Dichloro-phenyl)-1-{4-[4-(1*H*-2-methylindol-3-yl)-piperidin-1-ylethyl]-piperidin-1-yl}-propenone;
- (E)-3-(3,4-Dichloro-phenyl)-1-{4-[4-(1*H*-4-hydroxyindol-3-yl)-piperidin-1-ylethyl]-piperidin-1-yl}-propenone;
- 10 10 (E)-3-(3,4-Dichloro-phenyl)-1-{4-[4-(1*H*-6-hydroxyindol-3-yl)-piperidin-1-ylethyl]-piperidin-1-yl}-propenone;
- (E)-3-(3,4-Dichloro-phenyl)-1-{4-[4-(1*H*-5-hydroxy-7-methylindol-3-yl)-piperidin-1-ylethyl]-piperidin-1-yl}-propenone;
- 15 15 (E)-3-(3,4-Dichloro-phenyl)-1-{4-[4-(1*H*-5-methylcarboxyindol-3-yl)-piperidin-1-ylethyl]-piperidin-1-yl}-propenone;
- (E)-3-(3,4-Dichloro-phenyl)-1-{4-[4-(1*H*-2,7-dimethylindol-3-yl)-piperidin-1-ylethyl]-piperidin-1-yl}-propenone;
- (E)-3-(3,4-Dichloro-phenyl)-1-{4-[4-(1*H*-7-ethylindol-3-yl)-piperidin-1-ylethyl]-piperidin-1-yl}-propenone;
- 20 20 (E)-3-(3,4-Dichloro-phenyl)-1-{4-[4-(1*H*-4,5-methylenedioxyindol-3-yl)-piperidin-1-ylethyl]-piperidin-1-yl}-propenone;
- (E)-3-(3,4-Dichloro-phenyl)-1-{4-[4-(1*H*-5-carboxyamidoindol-3-yl)-piperidin-1-ylethyl]-piperidin-1-yl}-propenone;
- 25 25 (E)-3-(3,4-Dichloro-phenyl)-1-{4-[4-(1*H*-5-acetamidoindol-3-yl)-piperidin-1-ylethyl]-piperidin-1-yl}-propenone;
- (E)-3-(3,4-Dichloro-phenyl)-1-{4-[4-(1*H*-5-aminoindol-3-yl)-piperidin-1-ylethyl]-piperidin-1-yl}-propenone;
- (E)-3-(3,4-Dichloro-phenyl)-1-{4-[4-(1*H*-5-ureidoindol-3-yl)-piperidin-1-ylethyl]-piperidin-1-yl}-propenone;
- 30 30 (E)-3-(3,4-Dichloro-phenyl)-1-{4-[4-(1*H*-6-trifluoromethylindol-3-yl)-piperidin-1-ylethyl]-piperidin-1-yl}-propenone;
- (E)-3-(3,4-Dichloro-phenyl)-1-{4-[4-(1*H*-5-ethylsulfonamidoindol-3-yl)-piperidin-1-ylethyl]-piperidin-1-yl}-propenone;
- 35 35 (E)-3-(3,4-Dichloro-phenyl)-1-{4-[4-(1*H*-6-aminoindol-3-yl)-piperidin-1-ylethyl]-piperidin-1-yl}-propenone;

- (E)-3-(3,4-Dichloro-phenyl)-1-{4-[4-(1*H*-5-hydroxyindol-3-yl)-piperidin-1-ylmethyl]-piperidin-1-yl}-propenone;
- (E)-3-(3,4-Dichloro-phenyl)-1-{4-[4-(1*H*-5-methanesulfonamidoindol-3-yl)-piperidin-1-ylmethyl]-piperidin-1-yl}-propenone;
- 5 (E)-3-(3,4-Dichloro-phenyl)-1-{4-[4-(1*H*-2-methylindol-3-yl)-piperidin-1-ylmethyl]-piperidin-1-yl}-propenone;
- (E)-3-(3,4-Dichloro-phenyl)-1-{4-[4-(1*H*-5-methylcarboxyindol-3-yl)-piperidin-1-ylmethyl]-piperidin-1-yl}-propenone;
- (E)-3-(3,4-Dichloro-phenyl)-1-{4-[4-(1*H*-2,7-dimethylindol-3-yl)-piperidin-1-ylmethyl]-piperidin-1-yl}-propenone;
- 10 (E)-3-(3,4-Dichloro-phenyl)-1-{4-[4-(1*H*-7-ethylindol-3-yl)-piperidin-1-ylmethyl]-piperidin-1-yl}-propenone;
- (E)-3-(3,4-Dichloro-phenyl)-1-{4-[4-(1*H*-4,5-methylenedioxyindol-3-yl)-piperidin-1-ylmethyl]-piperidin-1-yl}-propenone;
- 15 (E)-3-(3,4-Dichloro-phenyl)-1-{4-[4-(1*H*-5-carboxyamidoindol-3-yl)-piperidin-1-ylmethyl]-piperidin-1-yl}-propenone;
- (E)-3-(3,4-Dichloro-phenyl)-1-{4-[4-(1*H*-5-acetamidoindol-3-yl)-piperidin-1-ylmethyl]-piperidin-1-yl}-propenone;
- (E)-3-(3,4-Dichloro-phenyl)-1-{4-[4-(1*H*-5-aminoindol-3-yl)-piperidin-1-ylmethyl]-piperidin-1-yl}-propenone;
- 20 (E)-3-(3,4-Dichloro-phenyl)-1-{4-[4-(1*H*-5-ureidoindol-3-yl)-piperidin-1-ylmethyl]-piperidin-1-yl}-propenone;
- (E)-3-(3,4-Dichloro-phenyl)-1-{4-[4-(1*H*-6-trifluoromethylindol-3-yl)-piperidin-1-ylmethyl]-piperidin-1-yl}-propenone;
- 25 (E)-3-(3,4-Dichloro-phenyl)-1-{4-[4-(1*H*-5-ethylsulfonamidoindol-3-yl)-piperidin-1-ylmethyl]-piperidin-1-yl}-propenone;
- (E)-3-(3,4-Dichloro-phenyl)-1-{4-[4-(1*H*-6-aminoindol-3-yl)-piperidin-1-ylmethyl]-piperidin-1-yl}-propenone;
- (E)-3-(2-Chloro-phenyl)-1-{4-[4-(1*H*-5-hydroxyindol-3-yl)-piperidin-1-ylmethyl]-piperidin-1-yl}-propenone;
- 30 (E)-3-(3,4-Dichloro-phenyl)-1-{4-[4-(1*H*-indol-3-yl)-piperidin-1-yl]-piperidin-1-yl}-propenone;
- (E)-3-(3,4-Dichloro-phenyl)-1-{4-[4-(1*H*-5-hydroxyindol-3-yl)-piperidin-1-ylpropyl]-piperidin-1-yl}-propenone;
- 35 exo-(E)-3-(3,4-Dichloro-phenyl)-1-{4-[3-(1*H*-indol-3-yl)-8-aza-bicyclo[3.2.1]oct-8-ylethyl]-piperidin-1-yl}-propenone;

- endo-(E)-3-(3,4-Dichloro-phenyl)-1-{4-[3-(1*H*-indol-3-yl)-8-aza-bicyclo[3.2.1]oct-8-ylethyl]-piperidin-1-yl}-propenone;
exo-(E)-3-(3,4-Dichloro-phenyl)-1-{4-[3-(1*H*-7-methylindol-3-yl)-8-aza-bicyclo[3.2.1]oct-8-ylethyl]-piperidin-1-yl}-propenone;
5 exo-(E)-3-(3,4-Dichloro-phenyl)-1-{4-[3-(1*H*-5-methoxyindol-3-yl)-8-aza-bicyclo[3.2.1]oct-8-ylethyl]-piperidin-1-yl}-propenone;
exo-(E)-3-(3,4-Dichloro-phenyl)-1-{4-[3-(1*H*-5-methanesulfonamidoindol-3-yl)-8-aza-bicyclo[3.2.1]oct-8-ylethyl]-piperidin-1-yl}-propenone;
exo-(E)-3-(3,4-Dichloro-phenyl)-1-{4-[3-(1*H*-5-hydroxyindol-3-yl)-8-aza-10 bicyclo[3.2.1]oct-8-ylethyl]-piperidin-1-yl}-propenone;
exo-(E)-3-(3,4-Dichloro-phenyl)-1-{4-[3-(1*H*-indol-3-yl)-8-aza-bicyclo[3.2.1]oct-8-ylethyl]-piperidin-1-yl}-propenone;
(+/-)-*trans*-1-(E)-3-(3,4-Dichloro-phenyl)-3-hydroxy-4-{4-[4-(1*H*-indol-3-yl)-piperidin-1-ylethyl]-piperidin-1-yl}-propenone;
15 (+/-)-*cis*-1-(E)-3-(3,4-Dichloro-phenyl)-3-hydroxy-4-{4-[4-(1*H*-indol-3-yl)-piperidin-1-ylethyl]-piperidin-1-yl}-propenone;
(+/-)-*trans*-1-(E)-3-(3,4-Dichloro-phenyl)-3-acetoxy-4-{4-[4-(1*H*-indol-3-yl)-piperidin-1-ylethyl]-piperidin-1-yl}-propenone; and
(+/-)-*trans*-1-(E)-3-(3,4-Dichloro-phenyl)-3-hydroxy-4-{4-[4-(1*H*-indol-3-yl)-piperidin-20 1-ylmethyl]-piperidin-1-yl}-propenone.

- Compounds of the present invention are antagonists of the MCP-1 (CC2RB) receptor and also inhibit MCP-1 stimulated chemotaxis in monocytes. As such they are expected to be of use in therapy, in particular in the treatment of inflammatory conditions with monocyte 25 and/or lymphocyte involvement, for instance inflammatory diseases such as arthritis and osteoarthritis, and diseases with a clear inflammatory component such as atherosclerosis and stroke. Accordingly, in a further aspect, the present invention provides a compound of formula (I) for use in therapy.
- 30 Further diseases which may be treatable with compounds of the present invention include, for instance, psoriasis, chronic contact dermatitis, inflammatory bowel disease, multiple sclerosis, sarcoidosis, idiopathic pulmonary fibrosis, dermatomyositis, skin pemphigoid and related diseases, glomerulonephritis, vasculitis, hepatitis, diabetes, allograft rejection, graft-versus-host diseases, stroke, inflammatory conditions of the brain such as Alzheimer's Disease, and acute and chronic inflammation.
- 35

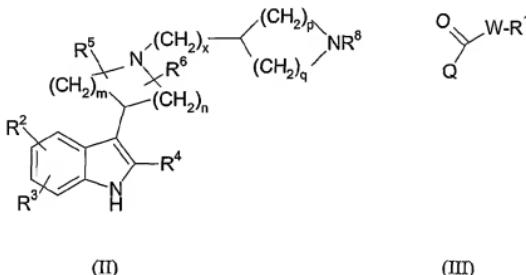
Compounds of the present invention may also be used to inhibit the entry of human immunodeficiency virus (HIV) into monocytes and lymphocytes , thereby having a therapeutic role in the treatment of AIDS.

- 5 In therapeutic use, the compounds of the present invention are usually administered in a standard pharmaceutical composition. The present invention therefore provides, in a further aspect, a pharmaceutical composition comprising a compound of formula (I) and a pharmaceutically acceptable carrier.
 - 10 Suitable pharmaceutical compositions include those which are adapted for oral or parenteral administration or as a suppository. The compounds of formula (I) which are active when given orally can be formulated as liquids, for example syrups, suspensions or emulsions, tablets, capsules and lozenges. A liquid formulation will generally consist of a suspension or solution of the compound or pharmaceutically acceptable salt in a suitable liquid carrier(s) for example, ethanol, glycerine, non-aqueous solvent, for example polyethylene glycol, oils, or water with a suspending agent, preservative, flavouring or colouring agent. A composition in the form of a tablet can be prepared using any suitable pharmaceutical carrier(s) routinely used for preparing solid formulations. Examples of such carriers include magnesium stearate, starch, lactose, sucrose and cellulose. A composition in the form of a capsule can be prepared using routine encapsulation procedures. For example, pellets containing the active ingredient can be prepared using standard carriers and then filled into a hard gelatin capsule; alternatively, a dispersion or suspension can be prepared using any suitable pharmaceutical carrier(s), for example aqueous gums, celluloses, silicates or oils and the dispersion or suspension then filled into a soft gelatin capsule. Typical parenteral compositions consist of a solution or suspension of the compound of formula (I) in a sterile aqueous carrier or parenterally acceptable oil, for example polyethylene glycol, polyvinyl pyrrolidone, lecithin, arachis oil or sesame oil. Alternatively, the solution can be lyophilised and then reconstituted with a suitable solvent just prior to administration.
 - 15
 - 20
 - 25
 - 30
 - 35
- A typical suppository formulation comprises a compound of formula (I) which is active when administered in this way, with a binding and/or lubricating agent such as polymeric glycols, gelatins or cocoa butter or other low melting vegetable or synthetic waxes or fats. Preferably the composition is in unit dose form such as a tablet or capsule.
- Each dosage unit for oral administration contains preferably from 1 to 500 mg (and for parenteral administration contains preferably from 0.1 to 25 mg) of a compound of the formula (I).

The daily dosage regimen for an adult patient may be, for example, an oral dose of between 1 mg and 1000 mg, preferably between 1 mg and 500 mg, or an intravenous, subcutaneous, or intramuscular dose of between 0.1 mg and 100 mg, preferably between

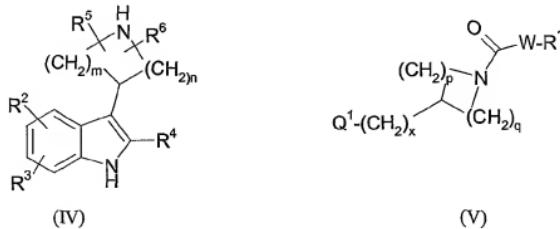
- 5 0.1 mg and 25 mg, of the compound of the formula (I), the compound being administered 1 to 4 times per day. Suitably the compounds will be administered for a period of continuous therapy, for example for a week or more.

Compounds of formula (I) may be prepared from convenient starting materials by adapting synthetic procedures well known in the art. Preferably, the final stage involves the formation of an amide bond between a compound of formula (II) and a compound of formula (III):



in which R¹ to R⁸, W, n, m and x are as hereinbefore defined and Q is hydroxyl or a leaving group such as chloride; or

- 20 alkylating or reductively alkylating the nitrogen of the central ring of a compound of formula (IV) with a compound of formula (V);



in which R¹ to R⁸, W n, m and x are as hereinbefore defined and Q¹ is a leaving group such as chloride, bromide or methanesulphonate, or Q¹ is part of an aldehyde function attached to the terminal carbon of (CH₂)_x.

- 5 Amide bond forming conditions are well known in the art and include reaction of the amine with an appropriate acid chloride in an inert solvent such as dichloromethane, optionally in the presence of a base such as triethylamine. Alternatively, the amine may be coupled directly with an appropriate carboxylic acid using a carbodi-imide such as 1-(3-dimethylaminopropyl)-3-ethylcarbodi-imide.

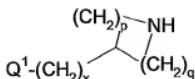
10 Alkylation conditions are well known in the art and include reaction of the amine with an appropriate alkylating agent in an inert solvent such as dimethylformamide, optionally with heating and optionally in the presence of an organic base such as triethylamine or an inorganic base such as sodium hydrogen carbonate.

15 Reductive alkylation conditions are well known in the art and include reaction of the amine with an appropriate aldehyde in the presence of a reducing agent, such as sodium triacetoxyborohydride, in an inert solvent such as dichloromethane.

20 Compounds of formulae (II) and (IV) are either commercially available or can be made from readily available precursors by using standard synthetic methodology, see for instance, Arz Forsch. 1985, 272. It will be appreciated that compounds of formula (II) may be readily obtained from compounds of formula (IV) by the alkylation thereof with an appropriate alkylating agent QXN* in which Q is a leaving group as hereinbefore defined and N* is a protected amine or a group transformable into an amine, for instance phthalimide, or by reductive alkylation with Q1XN*, where Q1 is part of an aldehyde function attached to the terminal carbon of X.

25 Compounds of formula (III) are carboxylic acids or derivatives thereof, for instances derivatives of (substituted) cinnamic acid, which are either commercially available *per se* or can be readily prepared from such using standard methodology (Comprehensive Organic Chemistry, vol 1, 1132). Compounds of formula (V) may be obtained by treating a compound of formula (III) with an appropriate amine of formula (VI):

30



(VI)

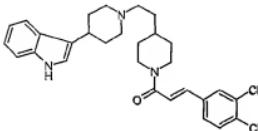
- in which R¹ to R⁸, W, n, m and x are as hereinbefore defined under amide bond forming conditions, as hereinbefore described in which Q' is a leaving group as hereinbefore described or a group convertible to a leaving group, or aldehyde.

The following Description and Examples illustrate the present invention.

Experimental

Example 1: (E)-3-(3,4-Dichloro-phenyl)-1-{4-[4-(1*H*-indol-3-yl)-piperidin-1-ylethyl]-piperidin-1-yl}-propenone

5



(a) N-tert-Butoxycarbonylamino-4-(2-hydroxyethyl)piperidine

4-(2-hydroxyethyl)piperidine (8g) was dissolved in acetonitrile (130ml) and treated with 10 a solution of Boe anhydride (13.5g) in acetonitrile (30ml). The solution was stirred for 5h, the solvent removed and the residue dissolved in citric acid. This was extracted with ethyl acetate, the latter dried over sodium sulphate and concentrated in vacuo to afford the title compound (10.12g).

15 (b) N-tert-Butoxycarbonylamino-4-(2-bromoethyl)piperidine

Triphenylphosphine (12.69g) was added in portions over 20 minutes to a solution of N-tert-Butoxycarbonylamino-4-(2-hydroxyethyl)piperidine (10.1g) and tetrabromomethane (16.07g) in dichloromethane (250ml). The solution was stirred for 1.5 hours then eluted through a silica gel plug. Evaporation of the eluant gave the title compound (11.0g).

20

(c) 1-(tert-Butoxycarbonylamino)-{4-[4-(1*H*-indol-3-yl)-piperidin-1-ylethyl]-piperidine

A stirred solution of 4-(indol-3-yl)-piperidine (2.36g) (Arz. Forsch. 1985, 272), N-tert-butoxycarbonylamino-4-(2-bromoethyl)piperidine (2.95g) and sodium bicarbonate (2.53g) in dimethylformamide (10mL) was heated at 80 °C for 18 hours. The solvent 25 was removed in vacuo and the residue treated with dilute sodium hydroxide solution and then extracted with dichloromethane (3x). The combined organic extracts were washed with water, then brine and dried over MgSO₄. Chromatography on silica gel eluting with 5% methanol in dichloromethane gave the title compound as a colourless oil (3.22g).

30 (d) 4-[4-(1*H*-indol-3-yl)-piperidin-1-ylethyl]-piperidine

To a stirred solution of 1-(tert-Butoxycarbonylamino)-{4-[4-(1*H*-indol-3-yl)-piperidin-1-ylethyl]-piperidine (3.1g) in dichloromethane (10mL) was added trifluoroacetic acid (10mL). The solution was stirred until effervescence ceased and then the solvent removed in vacuo. The residue was treated with dilute sodium hydroxide solution and

extracted with dichloromethane (3x). The combined organic extracts were washed with brine, dried over sodium sulphate and the solvent removed to give the title compound as a white solid foam (2.23g).

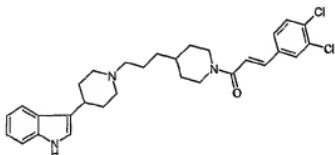
5 (e) **(E)-3-(3,4-Dichloro-phenyl)-1-{4-[4-(1H-indol-3-yl)-piperidin-1-ylethyl]-piperidin-1-yl}-propenone**

A solution of 4-[4-(1H-indol-3-yl)-piperidin-1-ylethyl]-piperidine (0.186g) in dichloromethane (20mL), and 2M sodium hydroxide solution was treated with 3,4-dichloro cinnamoylchloride (0.183g). After stirring overnight at room temperature, the

10 mixture was diluted with dichloromethane (100mL) and washed with 2M aqueous sodium hydroxide solution. The organic layer was dried over sodium sulphate and evaporated to dryness. Chromatography of the residue on silica gel using 2-10% methanol/dichloromethane as eluant afforded the title compound (0.2g) as a white solid foam.

15 Mass spectrum MH^+ 510/512. 1H NMR: δ (CDCl₃) 1.1-1.3 (2H, m), 1.5-2.0 (7H, m), 2.0-2.2 (4H, m), 2.3-2.6 (2H, n), 2.6-2.9 (2H, m), 3.1-3.3 (3H, m), 4.1 (1H, br d), 4.7 (1H, br d), 6.8 (1H, d), 6.9 (1H, t), 7.0 (1H, t), 7.1-7.7 (9H, m), 8.0 (1H, s).

Example 2: (E)-3-(3,4-Dichloro-phenyl)-1-{4-[4-(1H-indol-3-yl)-piperidin-1-ylpropyl]-piperidin-1-yl}-propenone



(a) **N-(3,4-Dichlorocinnamoyl)-4-(3-hydroxypropyl)piperidine**

25 A solution of 4-(3-hydroxypropyl)piperidine (3.42g) in dichloromethane (60mL) and 2M sodium hydroxide solution (60mL) was treated with 3,4-dichloro cinnamoylchloride (6.0g). After stirring overnight at room temperature, the mixture was diluted with dichloromethane (100mL) and washed with 2M aqueous sodium hydroxide solution and brine. The organic layer was dried over sodium sulphate and evaporated to dryness.

30 Chromatography of the residue on silica gel using 0-5% methanol/dichloromethane as eluant afforded the title compound (5.2g) as a colourless glass.

(b) **N-(3,4-Dichlorocinnamoyl)-4-(oxopropyl)piperidine**

To a stirred solution of oxalyl chloride (1.6ml) in THF (150mL) under argon at -78°C was added dropwise a solution of DMSO (2.5ml) in THF (20mL). After ca 10 minutes, a solution of N-(3,4-dichlorocinnamoyl)-4-(3-hydroxypropyl)piperidine (4.9g) in THF (100mL) and DMSO (7.5ml) was added dropwise over 40 minutes. After stirring for a further 2 hours at -78 °C, triethylamine (12ml) was added and the solution then allowed to warm to 0°C. Water was added and the organic phase concentrated and taken up in ethyl acetate. This was washed with 1M HCl, potassium bicarbonate solution and brine and dried over MgSO₄. Concentration in vacuo followed by trituration with ether afforded the title compound (4.1g) as a white solid.

10

(c) (E)-3-(3,4-Dichloro-phenyl)-1-{4-[4-(1H-indol-3-yl)-piperidin-1-ylpropyl]-piperidin-1-yl}-propenone

To a stirred solution of 4-(indol-3-yl)piperidine (118mg) (Arz. Forsch. 1985, 272) and N-(3,4-dichlorocinnamoyl)-4-(3-oxopropyl)piperidine (170mg) in 1,2-dichloroethane

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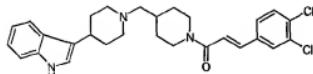
(10mL) was added sodium triacetoxyborohydride (250mg) and triethylamine (1ml). This was vortexed at room temperature for 4hours, poured into dilute sodium hydroxide solution and extracted with dichloromethane. The combined organic extracts were washed with water, then brine and dried over sodium sulphate. Concentration in vacuo and trituration with ethyl acetate/ether afforded the title compound (167mg) as a white solid.

20

Mass spectrum MH⁺ 524/526. ¹H NMR: δ (DMSO-d₆) 1.0-1.2 (2H, m), 1.2-1.3 (2H, m), 1.4-1.6 (3H, m), 1.6-1.8 (4H, m), 1.9-2.1 (3H, m), 2.28 (2H, t), 2.55-2.8 (2H, m), 2.95-3.1 (3H, m), 4.26 (1H, br d), 4.45 (1H, br d), 6.8 (1H, d), 6.94 (1H, t), 7.0-7.1 (2H, m), 7.35 (1H, d), 7.4 (1H, m), 7.5 (1H, d), 7.6 (2H, m), 8.1 (1H, s), 10.75 (1H, s).

25

Example 3: (E)-3-(3,4-Dichloro-phenyl)-1-{4-[4-(1H-indol-3-yl)-piperidin-1-ylmethyl]-piperidin-1-yl}-propenone



30

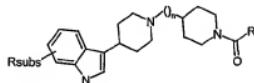
Following the procedures of Example 1(a)-1(e), but starting from 4-(2-hydroxymethyl)piperidine in place of 4-(2-hydroxyethyl)piperidine, the title compound was prepared.

Mass spectrum MH^+ 496/498. 1H NMR: δ (DMSO-d₆) 0.9-1.3 (2H, m), 1.6-2.0 (7H, m), 2.0-2.2 (2H, m), 2.3 (2H, d), 2.6-2.8 (2H, m), 3.0 (2H, m), 3.15 (1H, t), 4.3 (1H, br d), 4.5 (1H, br d), 6.95 (1H, t), 7.0-7.1 (2H, m), 7.2 (1H, d), 7.4 (2H, m), 7.5 (1H, m) 7.6-7.8 (2H, m), 8.1 (1H, s), 10.75 (1H, s).

5

Examples 4-40

Following the procedures of Example 2, using the appropriate 4-(3-hydroxyalkyl)piperidine and substituted cinnamoyl chloride intermediates consistent with
10 the final products, Examples 4-40 were prepared.

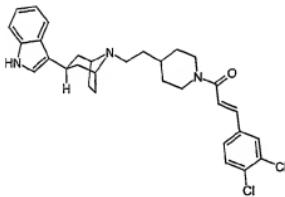


	Example	R_{sub5}	n	R
	4	5-OH	2	
	5	5-Me	2	"
	6	5-OMe	2	"
	7	5-MeSO ₂ NH	2	"
	8	7-Me	2	"
	9	2-Me	2	"
	10	4-OH	2	"
	11	6-OH	2	"
	12	5-OH, 7-Me	2	"
	13	5-COOMe	2	"
	14	2,7-diMe	2	"
	15	7-Et	2	"
	16	5,6-OCH ₂ O	2	"
	17	5-CONH ₂	2	"
	18	5-MeCONH	2	"
	19	5-NH ₂	2	"
	20	5-H ₂ NCONH	2	"
	21	6-CF ₃	2	"
	22	5-EtSO ₂ NH	2	"
	23	6-NH ₂	2	"

	24	5-OH	1	"
	25	5-MeSO ₂ NH	1	"
	26	2-Me	1	"
	27	5-COOMe	1	"
	28	2,7-diMe	1	"
	29	7-Et	1	"
	30	5,6-OCH ₂ O	1	"
	31	5-CONH ₂	1	"
	32	5-MeCONH	1	"
	33	5-NH ₂	1	"
	34	5-H ₂ NCONH	1	"
	35	6-CF ₃	1	"
	36	5-EtSO ₂ NH	1	"
	37	6-NH ₂	1	"
	38	H	1	
	39	H	0	
	40	5-OH	3	

Example 41: exo-(E)-3-(3,4-Dichloro-phenyl)-1-{4-[3-(1*H*-indol-3-yl)-8-aza-bicyclo[3.2.1]oct-8-ylethyl]-piperidin-1-yl}-propenone

5



(a) 3-(1H-Indol-3-yl)-8-aza-bicyclo[3.2.1]oct-2-ene-8-carboxylic acid tert-butyl ester

To a solution of sodium (1.92 g) in methanol (40 mL) was added indole (1.73 g) followed

10 by commercially available BOC-nortropinone (10 g). The mixture was refluxed under argon for 48h, then cooled to -10°C. Filtration of the precipitate afforded the title compound (2.7 g). Mass spectrum MH⁺ 325.

(b) Mixture of endo and exo 3-(1H-Indol-3-yl)-8-aza-bicyclo[3.2.1]octane-8-carboxylic acid tert-butyl ester

A solution of the compound of example 41(a) (1.9 g) in ethanol (100 mL) was hydrogenated over 10% palladium on charcoal (0.4 g) at 50°C and 50 psi for 18h.

- 5 Filtration followed by evaporation of the solvent afforded the crude product, which was purified by chromatography on silica using 30% ethyl acetate/hexane as eluent to afford the title compounds as a mixture of isomers (1.2 g). Mass spectrum $M^+ \text{-H}$ 325.

(c) Mixture of endo and exo 3-(8-aza-bicyclo[3.2.1]oct-3-yl)-1H-indole hydrochloride

- 10 The BOC derivative of example 41(b) (1.1 g) was dissolved in ethanolic HCl (20 mL) and the solution stirred for 2h. Evaporation of the solvent afforded the title compounds as a mixture of isomers (1.0 g). Mass spectrum MH^+ 227.

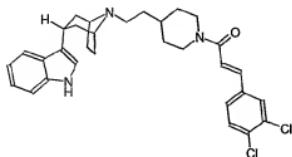
(d) Mixture of endo and exo (E)-3-(3,4-Dichloro-phenyl)-1-{4-[3-(1H-indol-3-yl)-8-aza-bicyclo[3.2.1]oct-8-ylethyl]-piperidin-1-yl}-propenone

- The compound of Example 41(c) (0.261 g) was reductively alkylkated with N-(3,4-dichlorocinnamoyl)-4-(2-oxoethyl)piperidine (0.326 g, prepared by analogous procedures to those described in Example 2 for N-(3,4-dichlorocinnamoyl)-4-(3-oxopropyl)piperidine) and sodium triacetoxyborohydride using the general procedure in Example 2. This afforded a mixture of exo and endo products.

(e) exo-(E)-3-(3,4-Dichloro-phenyl)-1-{4-[3-(1H-indol-3-yl)-8-aza-bicyclo[3.2.1]oct-8-ylethyl]-piperidin-1-yl}-propenone

- 25 Chromatography of the mixture of Example 41(d) on silica using 8% methanol-0.6% aqueous ammonia-91.4% dichloromethane as eluant afforded the desired exo isomer as the faster running band (0.13 g).

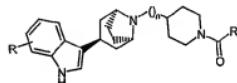
Example 42: endo-(E)-3-(3,4-Dichloro-phenyl)-1-{4-[3-(1H-indol-3-yl)-8-aza-bicyclo[3.2.1]oct-8-ylethyl]-piperidin-1-yl}-propenone



Further elution of the mixture from Example 41(d) afforded the endo isomer (0.015 g).

Examples 43-47

- 5 By analogous procedures to those described for Example 41, using the appropriately substituted indole consistent with the final product, Examples 43-47 were prepared.

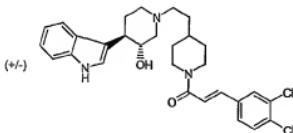


Example	R subs	n	R
43	7-Me	2	
44	5-OMe	2	
45	5-MeSO2NH	2	
46	5-OH	2	
47	H	1	

10

Example 48: (+/-)-trans-1-(E)-3-(3,4-Dichloro-phenyl)-3-hydroxy-4-{4-[4-(1*H*-indol-3-yl)-piperidin-1-ylethyl]-piperidin-1-yl}-propanone

15



Using (+/-)-trans-3-hydroxy-4-(3-indolyl)-piperidine (K. Freter, V. Fuchs, *J. Het. Chem.*, 1982, 19, 377) and N-(3,4-dichlorocinnamoyl)-4-(2-oxoethyl)piperidine in the reductive

20 alkylation procedure of Example 2(c), the title compound was prepared.

MS calcd for $(C_{28}H_{31}N_3O_2Cl_2 + H)^+$: 528. Found: 528.

1H NMR δ ($CDCl_3$) 8.33 (s, 1H), 7.72 (d, 1H), 7.59 (s, 1H), 7.53 (d, 1H), 7.43 (d, 1H), 7.37 (d, 1H), 7.31 (dd, 1H), 7.20 (t, 1H), 7.13-7.08 (m, 2H), 6.89 (d, 1H), 4.69 brd, 1H), 4.06 (brd, 1H), 3.93 (m, 1H), 3.25 (m, 1H), 2.91 (d, 1H), 2.80-2.64 (m, 2H), 2.55-2.42 (m, 2H), 2.15-1.72 (m,

5 7H), 1.69-1.59 (m, 1H), 1.58-1.48 (m, 2H), 1.30-1.15 (m, 2H).

Description 1: (+/-)-*cis*-3-hydroxy-4-(3-indolyl)-piperidine

(a) (+/-)-*cis* 1-tosyl-3-hydroxy-4-(3-indolyl)-piperidine

10 (+/-)-*trans* 1-tosyl-3-hydroxy-4-(3-indolyl)-piperidine (0.4g) (K. Freter, V. Fuchs, *J. Het. Chem.*, 1982, 19, 377) was suspended in a solution of toluene (10ml) before PPb_3 (0.59g) and chloroacetic acid (0.24g) were added. DEAD (0.35ml) was then added dropwise and the resulting yellow solution was stirred for 20h. The reaction mixture was concentrated and purified by column chromatography (25% EtOAc-hexane) to afford the title

15 compound as a white solid.

(b) (+/-)-*cis*-3-hydroxy-4-(3-indolyl)-piperidine

The intermediate of Description 1(a) was directly suspended in 1-BuOH (50ml) before sodium metal (1.2g) was added and the mixture was stirred at reflux for 2h. The reaction mixture was cooled, poured into water and extracted with EtOAc. After concentration the product crystallised to afford opaque crystals (0.25g).

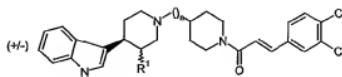
MS calcd for $(C_{13}H_{16}N_2O + H)^+$: 217. Found: 217.

1H NMR δ ($CDCl_3$) 8.21(brs, 1H), 7.71 (d, 1H), 7.38 (d, 1H), 7.24-7.09 (m, 3H), 3.98-3.81 (m, 1H), 3.28-3.22 (m, 2H), 2.98-2.82 (m, 3H), 2.12-2.08 (m, 1H), 1.62-1.54 (m, 1H).

25

Examples 49-51

By analogous procedures to those described in Example 2(c), but using the appropriate substituted indolopiperidine consistent with the final products, Examples 49-51 were prepared.



Example	R¹	n
49	cis 3-OH	2
50	trans 3-OAc	2
51	trans 3-OH	1

Description 2: Preparation of compounds by automated array synthesis

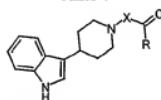
Automated synthesis was carried out using an Advanced Chem Tech 496 MOS robot.

- 5 Each reaction cell was charged with 1.2mL of a 0.15M solution of the acid component (0.18mmol) in THF (DMF was substituted as solvent if the acid was not soluble in THF). The robot then added 0.6mL of a solution containing 0.2M N,N'-diisopropylcarbodiimide (0.12mmol) and 0.2M 1-hydroxybenzotriazole (0.12mmol) in DMF, and the mixture was vortexed for 10 minutes. 0.6mL of a 0.1M solution of the amine component (0.6mmol)
- 10 in DMF was then added and the solution was vortexed for 18 hours. Work-up was carried out using a Hamilton Microlab 2200 SPE robot using solid phase extraction cartridges containing SCX (0.5g) as the solid phase. The cartridge was conditioned with 20% tetrahydrofuran/methanol then the solutions were transferred from the ACT reaction block to the extraction cartridge. The cartridges were then eluted with 20%
- 15 tetrahydrofuran/methanol (3 x 1.7ml) followed by a solution of 0.1M aqueous ammonia in methanol (1.5ml) and the eluant was discarded. Elution with a solution of 1M aqueous ammonia in methanol (4.5ml) and evaporation of the eluant gave the desired compound.

Examples 52-147

20

Using the automated array procedure of Description 2, Examples 52-147 were prepared. ¹H NMR spectra and mass spectra were consistent with the structures in Table 1.

Table 1

25

X \ R		52	53	54	55	56	57	58	59

X \ R		60	61	62	63	64	65	66	67

									
	68		69		70		71		72
			74		75				

									
	76		77		78		79		80
			(CH ₂) ₄ CH ₃						

									
	82		83		84		85		86
			87						89
	90		91		92		93		94
			95						97

									
	98		99		100		101		102
			103		104				105
	106		107		108		109		110
			111						112

5

									
	114		115		116		117		118
			119		120				121
	122		123		124		125		126
			127						128

									
	130		131		132		133		134
			135		136				137
	138		139		140		141		142
			143						145

	146						
	147						

Spectral Data

Example	Spectral Data
4	Mass spectrum MH^+ 526/528. 1H NMR: δ DMSO 0.95-1.2 (2H, m), 1.3-1.5 (2H, m), 1.55-1.8 (5H, m), 1.85 (2H, m), 1.95 (2H, m), 2.3 (2H, t), 2.55-2.7 (2H, m), 2.95 (2H, m), 3.05 (1H, t), 4.25 (1H, br d), 4.45 (1H, br d), 6.45 (1H, d), 6.82 (1H, s), 6.95 (1H, s) 7.1 (1H, m), 7.4 (2H, m), 7.62 (1H, m), 7.7 (1H, d), 8.1 (1H, s), 8.5, (1H br s), 10.75 (1H, s).
7	Mass spectrum MH^+ 603/605. 1H NMR: δ DMSO 0.9-1.2 (2H, m), 1.3-1.5 (2H, m), 1.6-1.8 (5H, m), 1.9-2.2 (4H, m), 2.3 (2H, t), 2.55-2.7 (2H, m), 2.88 (3H, s), 2.9-3.1 (4H, m), 4.3 (1H, br d), 4.45 (1H, br d), 6.98 (1H, d) 7.1 (1H, m), 7.3 (1H, d), 7.4 (2H, m), 7.85 (1H, d), 7.72 (1H, d), 8.1, (1H s), 9.15 (1H, s) 10.8 (1H, s).
12	Mass spectrum MH^+ 540/542. 1H NMR: δ D-6 DMSO 1.06 (2H, m), 1.42 (2H, b d), 1.5-1.8 (4H, m), 1.86 (2H, d), 1.99 (2H, t), 2.22 (3H, s), 2.28 (1H, m), 2.5-2.7 (2H, m), 2.98 (2H, d), 3.08 (1H, t), 3.4 (2H, m), 4.28 (1H, d), 4.45 (1H, d), 6.39 (1H, s), 6.66 (1H, s), 6.94 (1H, s), 7.41 (2H, m), 7.63 (1H, d), 7.71 (1H, d), 8.10 (1H, s), 8.47 (1H, b s), 10.41 (1H, s).
19	Mass spectrum MH^+ 525/527. 1H NMR: δ D-6 DMSO 0.97-1.1.16 (2H, m), 1.35-1.48 (2H, m), 1.50-1.84 (5H, m), 1.88 (2H, d), 1.93-2.11 (2H, br t), 2.30-2.41 (2H, m), 2.52-2.68 (2H, m), 2.97 (2H, br d), 3.06 (1H, app t), 4.23-4.88 (4H, m), 6.45 (1H, dd), 6.69 (1H, d), 6.87 (1H, d), 7.01 (1H, d), 7.36-7.45 (2H, m), 7.65 (d, 1H), 7.70 (1H, d), 8.11 (1H, s), 10.22 (1H, br s).
22	Mass spectrum MH^+ 617/619. 1H NMR: δ D-6 DMSO 0.96-1.18 (2H, m), 1.21 (3H, t), 1.37-1.50 (2H, m), 1.54-1.82 (5H, m), 1.83-1.95 (2H, m), 1.96-2.12 (2H, m), 2.32-2.45 (2H, m), 2.58-2.76 (2H, m), 2.95 (2H, q), 2.91-3.04 (3H, m), 3.25-4.37 (1H, m), 4.38-4.50 (1H, m), 6.99 (1H, dd), 7.13 (1H, d), 7.29 (1H, d), 7.35-7.46 (3H, m), 7.65-7.71 (2H, m), 8.12 (1H, m), 9.27 (1H, s), 10.80 (1H, br s).
24	Mass spectrum MH^+ 512/514. 1H NMR: δ DMSO 0.9-1.2 (2H, m), 1.55-1.7 (2H, m), 1.8-1.95 (5H, m), 2.0 (2H, m), 2.2 (2H, m), 2.6-2.75 (2H, m), 2.9 (2H, m), 3.1 (1H, t) 4.3 (1H, br d), 4.45 (1H, br d), 6.55 (1H, m) 6.85 (1H, d) 6.98 (1H, d) 7.1 (1H, d), 7.4 (2H, m), 7.65 (1H, d), 7.72 (1H, d), 8.1, (1H s), 8.5 (1H, s) 10.4 (1H, s).

25	Mass spectrum MH ⁺ 589/591. ¹ H NMR: δ DMSO 0.9-1.2 (2H, m), 1.6-1.9 (9H, m), 2.1 (2H, t), 2.2 (2H, m), 2.6-2.75 (1H, m) 2.84 (3H, s), 2.95 (2H, m), 3.05 (1H, m) 4.25 (1H, br d), 4.45 (1H, br d), 6.98 (1H, d) 7.1 (1H, m), 7.3 (1H, d), 7.4 (2H, m), 7.65 (1H, d), 7.72 (1H, d), 8.1, (1H s), 9.15 (1H, s) 10.8 (1H, s).
32	Mass spectrum MH ⁺ 553/555. ¹ H NMR: δ D-6 DMSO 0.92-1.13 (2H, m), 1.60-1.95 (7H, m), 1.96-2.10 (5H, m), 2.18 (2H, d), 2.57-2.75 (2H, m), 2.94-2.96 (2H, m), 3.08 (1H, app t), 4.29 (1H, m), 4.46 (1H, m), 7.06 (1H, s), 7.17-7.23 (2H, m), 7.34-7.43 (2H, m), 7.64-7.72 (2H, m), 7.80 (1H, s), 8.11 (1H, s), 9.68 (1H, s), 10.67 (1H, s).
33	Mass spectrum MH ⁺ 509/511. ¹ H NMR: δ D-6 DMSO 0.93-1.12 (2H, m), 1.50-1.92 (7H, m), 1.93-2.18 (2H, d), 2.50-2.74 (3H, m), 2.93 (2H, m), 3.08 (1H, app t), 4.22-4.58 (4H, m), 6.45 (1H, d), 6.69 (1H, s), 6.89 (1H, s), 7.01 (1H, d), 7.35-7.45 (2H, m), 7.60-7.72 (2H, m), 8.31 (1H, s), 10.22 (1H, s).
34	Mass spectrum MH ⁺ 554/556. ¹ H NMR: δ D-6 DMSO 0.92-1.20 (2H, m), 1.59-2.28 (11H, m), 2.59-2.73 (2H, m), 2.90-3.04 (2H, m), 3.10 (1H, app t), 4.33 (2H, m), 4.47 (1H, m), 5.61 (2H, s), 7.03 (2H, m), 7.19 (1H, d), 7.36-7.49 (2H, m), 7.58 (1H, s), 7.61-7.72 (2H, m), 8.12 (1H, s), 8.22 (1H, s), 10.56 (1H, br s).
36	¹ H NMR: δ D-6 DMSO 0.95-1.25 (2H, m), 1.20 (3H, t), 2.30-2.58 (11H, m), 2.43-2.58 (1H, m), 2.59-2.80 (m, 1H), 2.95 (2H, q), 2.82-3.20 (3H, m), 4.26-4.51 (2H, m), 6.99 (1H, d), 7.15 (1H, d), 7.30 (1H, d), 7.37-7.48 (3H, m), 7.63-7.73 (2H, m), 8.13 (1H, s), 9.28 (1H, br s).
41	Mass spectrum MH ⁺ 536/538. ¹ H NMR: δ CDCl ₃ 1.25 (2H, m), 1.65 (4H, m), 1.84 (5H, m), 1.95 (2H, t), 2.06 (2H, m), 2.49 (2H, m), 2.70 (1H, t), 3.14 (1H, t), 3.28 (1H, m), 3.35 (2H, s), 4.08 (1H, d), 4.69 (1H, d), 6.89 (1H, d), 6.99 (1H, s), 7.10 (1H, dd), 7.20 (1H, dd), 7.35 (2H, m), 7.43 (1H, d), 7.52 (1H, d), 7.61 (1H, s), 7.67 (1H, d), 7.9 (1H, s).
42	Mass spectrum MH ⁺ 536/538. ¹ H NMR: δ CDCl ₃ 1.23 (2H, m), 1.45-1.75 (8H, m), 1.89 (4H, m), 2.45 (3H, m), 2.72 (1H, t), 3.15 (1H, t), 3.30 (1H, m), 3.42 (1H, m), 4.08 (1H, d), 4.68 (1H, d), 6.89 (1H, d), 7.01 (2H, s), 7.19 (1H, dd), 7.35 (2H, m), 7.45 (1H, d), 7.55 (1H, d), 7.62 (2H, m), 7.99 (1H, s).

Biological Data**1. Cell membrane assay, using membranes from transfected CHO cells expressing the CCR2B (MCP-1) receptor.**

- 5 (a) Generation of CCR2B cell line – A fragment containing a Kozak sequence and the CCR2B coding sequence (ref Berkhou et al, J Biol Chem, 1997, 272, 16404 and references cited therein) was subcloned into the mammalian expression vector pCDN (Aiyar N, Baker E, Wu H-L, Nambi P, Edwards R M, Trill J, Ellis C and Bergsma D J, Human ATI receptor is a single copy gene : Characterisation in a stable cell line, Mol 10 Cell Biochem, 131, 75-86, 1994). The resulting construct was sequenced to confirm the sequence integrity of CCR2B. Stable cell lines were obtained by electroporation of the pCDN:CCR2B vector into Chinese Hamster Ovary (CHO) cells, followed by clonal selection using G418. The resulting clones were screened for high-level receptor expression by ligand binding assays on whole cells. From this screen, the clonal cell line 15 producing the highest number of receptors per cell was chosen for further studies.
- 15 (b) ^{125}I - labelled MCP-1 (Amersham International, UK) was incubated with membrane suspension (25 μg of protein) in the presence or absence of increasing concentrations of unlabelled human MCP-1 (R + D Systems) or antagonist for 2 hours at room temperature in a 96-well plate with 50 mM HEPES 1mM CaCl_2 , 5mM MgCl_2 , BSA (0.5% w/v final 20 conc), pH 7.4.

Following incubation, the membranes were washed and collected onto a 96 well polyethylenimine-treated Packard GF/C filter, using a Packard harvester. The plate was oven dried and radioactivity bound to the filter plate was counted using a Topcount liquid scintillation counter. The IC_{50} values and pK_i values were calculated using Inflexion, a 25 non-linear iterative curve fitting program based on Microsoft Excel (Br J Pharmacol, 1994, 112, 440P)

The compounds of the Examples had pK_i values in the range 5-7.5.

30 2. Monocyte Chemotaxis**(a) Monocyte isolation**

Human peripheral blood monocytes were prepared from the blood of normal healthy volunteers, essentially as described by Boyum (1984, *Methods in Enzymology* (Academic Press, New York and London) 108, 88-102). Blood was collected into anticoagulant (one part 50mM EDTA, pH 7.4, to nine parts blood), then centrifuged for 5 minutes at 600g. The upper layer of platelet-rich plasma was removed and centrifuged for 15 minutes at 900g, to pellet the platelets. The upper layer of platelet-poor plasma was removed and

added back to the packed red cells; the pelleted platelets were discarded. Dextran T500 was added (10 volumes EDTA blood to one volume 6% (w/v) dextran in 0.9% (w/v) NaCl) and the erythrocytes were allowed to sediment at unit gravity for 30 minutes. The resultant leukocyte-rich plasma was removed and centrifuged for 5 minutes at 400g. The

- 5 cell pellet was resuspended in 5ml of the supernatant, and the suspension was underlayered with 3ml NycoPrep, then centrifuged for 15 minutes at 600g. The mononuclear layer at the interface between the plasma and the NycoPrep was removed and washed through PBS by centrifugation for 5 minutes at 400g. The mononuclear layer typically contained $\geq 80\%$ monocytes, determined by staining cytocentrifuge preparations
10 for non-specific esterase using α -naphthyl-butyrate. Cell viability (typically >95%) was assessed as the ability to exclude trypan blue.

(b) **Chemotaxis**

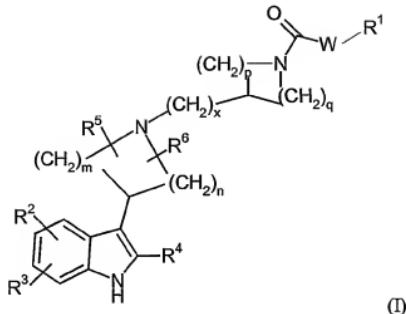
The ability of the MCP-1 antagonists to inhibit the chemoattractant activity of MCP-1 towards freshly isolated human monocytes was determined using a 48-well modified

- 15 Boyden microchemotaxis chamber. MCP-1 (1nM), was incubated with varying concentrations of the antagonist, and aliquots of these mixtures were placed in the lower wells of the chamber. Monocytes were also incubated with varying concentrations of antagonist and aliquots of these mixtures were placed in the upper wells of the chamber, such that the same concentration of the antagonist was present in both the upper and
20 corresponding lower wells. Numbers of cells migrating from the upper chamber across a polycarbonate filter (5 μ m pore size) following incubation at 37°C and 5% CO₂ humidified air were quantified by light microscopy of Diff-Quik stained filters, using a x40 objective and x10 ocular containing a 10mm² counting grid. Dose-inhibition curves were constructed, and from these, pK_b values were determined.
25 For chemotaxis with immortalised or transfected cell lines, essentially the same format was used, except that a 96-well chemotaxis chamber was employed. Cells which have migrated across a polycarbonate filter (5 μ m pore size) following incubation at 37°C and 5% CO₂ humidified air were quantified colorimetrically from a standard curve relating cell density to absorbance at 590nm. The colorimetric end point derives from cellular
30 reduction of 3-[4,5, dimethylthiazol-2-yl]-2,5, diphenyltetrazolium bromide from its formazan product.

The compounds of the Examples had pK_b's in the range 5-7.6.

Claims

1. A compound of the formula (I):



5

in which:

- R¹ is (C₁-6)alkyl, optionally substituted aryl or optionally substituted heteroaryl;
- R² and R³ which may be the same or different are selected from the group consisting of hydrogen, halogen, cyano, (C₁-6)alkyl, (C₃-7)cycloalkyl, (C₁-6)alkoxy, halo(C₁-6)alkyl, hydroxy, amino, mono- or di-(C₁-6)alkylamino, acylamino, nitro, carboxy, (C₁-6)alkoxycarbonyl, (C₁-6)alkenylloxycarbonyl, (C₁-6)alkoxycarbonyl(C₁-6)alkyl, carboxy(C₁-6)alkyl, (C₁-6)alkylcarbonyloxy, carboxy(C₁-6)alkyloxy, (C₁-6)alkoxycarbonyl(C₁-6)alkoxy, (C₁-6)alkylthio, (C₁-6)alkylsulphanyl, (C₁-6)alkylsulphonyl, sulphamoyl, mono- and di-(C₁-6)-alkylsulphamoyl, carbamoyl, mono- and di-(C₁-6)alkylcarbamoyl, ureido, (C₁-6)alkylsulphonamido, arylsulphonamido, aryl, aryl(C₁-6)alkyl, aryl(C₁-6)alkoxy, aryloxy and heterocycl;
- R⁴ is hydrogen or C₍₁₋₆₎alkyl;
- R⁵ and R⁶ which may be the same or different are hydrogen or C₍₁₋₆₎alkyl, or together with the carbon atoms of the ring to which they are attached form a bridging 5- to 7-membered ring;
- W is a bond, (C₁-6)alkylene optionally substituted by (C₁-6)alkyl, CH₂O, CH₂S or trans-(E)-CR⁷=CH-Y- in which R⁷ is hydrogen or (C₁-6)alkyl and Y is a bond, trans-(E)-CH=CH-, or CO;
- m and n are each integers from 1 to 3;
- p and q are each independently 1 or 2; and
- x is an integer from 1 to 4; or

a pharmaceutically acceptable salt thereof.

2. A pharmaceutical composition comprising a compound as defined in claim 1 together with a pharmaceutically acceptable carrier or excipient.

5

3. A compound as defined in claim 1 for use in therapy.

4. A compound as defined in claim 1 for use in the treatment of atherosclerosis or arthritis.

10

5. Use of a compound as defined in claim 1 in the manufacture of a medicament for use in the treatment of inflammatory conditions with monocyte and/or lymphocyte involvement.

15

6. A process for preparing a compound of formula (I) as defined in claim 1 which process comprises:

INTERNATIONAL SEARCH REPORT

Inb
al Application No
PCT/EP 02/03572

A. CLASSIFICATION OF SUBJECT MATTER
IPC 7 C07D401/14 C07D451/02 A61K31/4545 A61P29/00

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

IPC 7 C07D

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

EPO-Internal, WPI Data, BEILSTEIN Data, CHEM ABS Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	WO 00 51607 A (PARSONS WILLIAM H ;BAKER ROBERT K (US); MERCK & CO INC (US); RUPPR) 8 September 2000 (2000-09-08) page 1, line 6 - line 16; claims 1,17,19 -----	1-5
A	WO 98 06703 A (CONNOR DAVID THOMAS ;WARNER LAMBERT CO (US); GLASE SHELLY ANN (US)) 19 February 1998 (1998-02-19) cited in the application page 27, line 13 - line 31; claims 1,12,13,17 -----	1-5

Further documents are listed in the continuation of box C.

Patent family members are listed in annex.

* Special categories of cited documents :

- *A* document defining the general state of the art which is not considered to be of particular relevance
- *E* earlier document but published on or after the International filing date
- *L* document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)
- *O* document referring to an oral disclosure, use, exhibition or other means
- *P* document published prior to the International filing date but later than the priority date claimed

T later document published after the International filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

X document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
Y document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art

Z document member of the same patent family

Date of the actual completion of the International search

Date of mailing of the International search report

8 August 2002

16/08/2002

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Authorized officer

Seelmann, I

FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

Continuation of Box I.2

Claims Nos.: 6

The wording of present claim 6 is incomplete to such an extend that it is unclear and no search is possible (Article 6 PCT).

The applicant's attention is drawn to the fact that claims, or parts of claims, relating to inventions in respect of which no international search report has been established need not be the subject of an international preliminary examination (Rule 66.1(e) PCT). The applicant is advised that the EPO policy when acting as an International Preliminary Examining Authority is normally not to carry out a preliminary examination on matter which has not been searched. This is the case irrespective of whether or not the claims are amended following receipt of the search report or during any Chapter II procedure.

INTERNATIONAL SEARCH REPORT

International application No.
PCT/EP 02/03572

Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This International Search Report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:

2. Claims Nos.: 6 because they relate to parts of the International Application that do not comply with the prescribed requirements to such an extent that no meaningful International Search can be carried out, specifically:

see FURTHER INFORMATION sheet PCT/ISA/210

3. Claims Nos.: _____
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

- As all required additional search fees were timely paid by the applicant, this International Search Report covers all searchable claims.
 - As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.
 - As only some of the required additional search fees were timely paid by the applicant, this International Search Report covers only those claims for which fees were paid, specifically claims Nos.:
 - No required additional search fees were timely paid by the applicant. Consequently, this International Search Report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

- The additional search fees were accompanied by the applicant's protest.

No protest accompanied the payment of additional search fees.